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ORIGINAL REPORT

Results of the Intergroup Rhabdomyosarcoma Study Group D9602 Protocol, Using Vincristine and Dactinomycin With or Without Cyclophosphamide and Radiation Therapy, for Newly Diagnosed Patients With Low-Risk Embryonal Rhabdomyosarcoma: A Report From the Soft Tissue Sarcoma Committee of the Children's Oncology Group

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See accompanying articles on pages 1304 and 1319

A B S T R A C T

Purpose
Patients with localized, grossly resected, or gross residual (orbital only) embryonal rhabdomyosarcoma (ERMS) had 5-year failure-free survival (FFS) rates of 83% and overall survival rates of 95% on Intergroup Rhabdomyosarcoma Study Group (IRSG) protocols III/IV. IRSG D9602 protocol (1997 to 2004) objectives were to decrease toxicity in similar patients by reducing radiotherapy (RT) doses and eliminating cyclophosphamide for the lowest-risk patients.

Patients and Methods
Subgroup A patients (lowest risk, with ERMS, stage 1 group I/IIA, stage 1 group III orbit, stage 2 group I) received vincristine plus dactinomycin (VA). Subgroup B patients (ERMS, stage 1 group IIB/C, stage I group III nonorbit, stage 2 group II, stage 3 group I/II) received VA plus cyclophosphamide. Patients in group II/III received RT. Compared with IRS-IV, doses were reduced from 41.4 to 36 Gy for stage 1 group IIA patients and from 50 or 59 to 45 Gy for group III orbit patients.

Results
Estimated 5-year FFS rates were 89% (95% CI, 84% to 92%) for subgroup A patients (n = 264) and 85% (95% CI, 74%, 91%) for subgroup B patients (n = 78); median follow-up: 5.1 years. Estimated 5-year FFS rates were 81% (95% CI, 68% to 90%) for patients with stage 1 group IIA tumors (n = 62) and 86% (95% CI, 76% to 92%) for patients with group III orbit tumors (n = 77).

Conclusion
Five-year FFS and OS rates were similar to those observed in comparable IRS-III patients, including patients receiving reduced RT doses, but were lower than in comparable IRS-IV patients receiving VA plus cyclophosphamide. Five-year FFS rates were similar among subgroups A and B patients.

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INTRODUCTION

The Intergroup Rhabdomyosarcoma Study Group (IRSG) was founded in 1972 to elucidate biology and improve therapy for patients younger than 21 years with newly diagnosed rhabdomyosarcoma (RMS) and undifferentiated soft tissue sarcoma. Sequential protocols were designated IRS-I through IRS-IV.[1-4]

In IRS-III and -IV,[3,4] separate treatment plans were developed for patients with a low risk of recurrence. Patients with localized embryonal rhabdomyosarcoma (ERMS) and stage 1 disease (favorable sites), group I (completely resected) and IIA (microscopic marginal disease with uninvolved regional lymph nodes, N0), and orbit tumors in group III (gross residual disease, N0), plus patients in stage 2, group I (other sites, completely resected tumors ≤ 5 cm in widest diameter, N0) had 5-year failure-free survival (FFS) rates of 78% to 89% and overall survival (OS) rates of higher than 90% after treatment with vincristine and dactinomycin (VA) with or without cyclophosphamide (C) with or without radiation therapy (RT). Subsequent similar patients were designated subgroup A in D9602. Other low-risk ERMS patients had stage 1 group III nonorbital

tumors, groups IIB/IIC (tumor-involved regional lymph nodes, designated N1, grossly resected without (B) or with (C) microscopic residual); stage 2 group II N1, and stage 3 groups I N0 and II, N0 or N1. Their 3-year FFS rate on IRS-III/IV was 88% and OS rate was 96%, when treated with VAC with or without radiation therapy (RT).[3,4] Subsequent similar patients were designated subgroup B in D9602.

Data from single institutions[5,6] demonstrated satisfactory local control of microscopic residual disease using RT doses down to 30 Gy, suggesting that reducing dose from 41.4 Gy, used in IRS-IV, would be feasible. Previous IRSG data showed no significant dose-response relationship with RT doses down to 40 Gy for group III orbit tumors.[7]

The D9602 low-risk protocol had three major objectives: to estimate FFS rates of patients in subgroup A after VA chemotherapy for 45 weeks, plus RT for patients with residual tumor; to estimate FFS rates of patients in subgroup B after VAC for 45 weeks, plus RT for patients with residual tumor; and to ascertain local control and FFS rates in three selected groups of patients given RT doses 5 to 10 Gy lower than in IRS-III/IV[3,4]: 36 Gy for stage 1 group IIA, 45 Gy for stage 1 group III N0 orbit, and 36 Gy for stages 2/3 group IIA patients.

PATIENTS AND METHODS

We used the IRSG staging system to account for previously observed differences in outcome according to primary tumor site, and the Surgico-pathologic Grouping system to categorize patients according to extent of disease at diagnosis, type of surgical procedure, and pathologic review of the surgical specimen.[4] Patients eligible for registration on D9602 were younger than 50 years, previously untreated, with a low risk of recurrence. Patients with ERMS or embryonal ectomesenchymoma in stage 1 groups I/IIA, group III orbit, and stage 2 group I were assigned to subgroup A. Patients with ERMS with stage 1 group III nonorbital tumors, groups IIB/C, stage 2 group II, and stage 3 group I/II were assigned to subgroup B. The local Human Investigations Committees approved the D9602 study for patient registration. The patient or guardian signed the informed consent form. Presurgical investigations and follow-up evaluations were similar to those previously reported,[4] as were reviews of records.

Treatment: Chemotherapy

Chemotherapy began within 42 days after diagnosis. Treatment schemas are shown in Table 1. Subgroup B patients received the same schedule of VA as patients in subgroup A, plus IV cyclophosphamide (C) with MESNA for uroprotection and injections of filgrastim (granulocyte colony-stimulating

Table 1. D9602 Treatment Regimens for Subgroup A Patients (without C/mesna and G-CSF) and for Subgroup B Patients (with C/mesna and G-CSF)

Week												
0	1	2	3	4	5	6	7	8	9	10	11	E
V	V	V	V	V	V	V	V	V	—	—	—	V
A	—	—	A	—	—	A*	—	—	A	—	—	A
C + G-CSF	—	—	C + G-CSF	—	—	C + G-CSF	—	—	C + G-CSF	—	—	L
			RT (if group II or III)									
Week												
12†	13	14	15	16	17	18	19	20‡	21	22	23	E
V	V	V	V	V	V	V	V	V	—	—	—	V
A	—	—	A*	—	—	A*	—	—	A	—	—	A
C + G-CSF	—	—	C + G-CSF	—	—	C + G-CSF	—	—	—	—	—	L
RT (if indicated)‡												
Week												
24†	25	26	27	28	29	30	31	32	33	34	35	E
V	V	V	V	V	V	V	V	V	—	—	—	V
A	—	—	A	—	—	A*	—	—	A*	—	—	A
C + G-CSF	—	—	C + G-CSF	—	—	C + G-CSF	—	—	—	—	—	L
			RT (if indicated)‡									
Week												
36†	37	38	39	40	41	42	43	44	45	46	47	E
V	V	V	V	V	V	V	V	V	—	—	—	V
A	—	—	A	—	—	A	—	—	A	—	—	A
C + G-CSF	—	—	C + G-CSF	—	—	C + G-CSF	—	—	—	—	—	L
Week												
48†												

Abbreviations: G-CSF, granulocyte colony-stimulating factor, 5 μg/kg subcutaneously every day or granulocyte-macrophage colony stimulating factor, 250 $\mu g/m^2$/day; C, cyclophosphamide: dose intravenously before August 2002, age $<$ 1 year: 1.1 g/m^2, age $>$ 1 year: 2.2 g/m^2, dose intravenously after December 2002, age $<$ 1 year: 36 mg/kg, age 1 to $<$ 3 years: 73 mg/kg, age $\geq$ 3 years: 2.2 g/m^2, given with MESNA; V, vincristine: dose intravenously before August 2002, age $<$ 1 year: 0.75 mg/m^2, $\geq$ 1 year: 1.5 mg/m^2 (maximum dose, 2 mg), dose after December 2002, age $<$ 1 year: 0.025 mg/kg, age 1 to $<$ 3 years: 0.05 mg/kg, age $\geq$ 3 years: 1.5 mg/m^2 (maximum dose, 2 mg); EVAL, evaluate extent of disease clinically and radiographically; A, dactinomycin dose intravenously before August 2002, age $<$ 1 year: 0.025 mg/kg, age $\geq$ 1 year and $\leq$ 30 kg: 0.045 mg/kg, age $>$ 1 year and $>$ 30 kg: 1.5 mg/m^2 (maximum dose, 2.5 mg), dose after December 2002, age $<$ 1 year: 0.025 mg/kg, age $\geq$ 1 year: 0.045 mg/kg (maximum dose, 2.5 mg); RT, conventional radiation therapy.

*Omit dactinomycin at week 6 in patients beginning RT at week 3, weeks 15 and 18 in patients beginning RT at week 12, and weeks 30 and 33 in patients beginning RT at week 28.

†Evaluation for all patients, including those with vaginal primaries (except week 24, if N0).

‡Patients with vaginal primaries and tumor-involved regional lymph nodes or with nonorbital, stage 1, group III tumors start RT at week 12. Patients with vaginal primaries and negative nodes start RT at week 28, if repeat biopsies show persistent viable tumor cells.

factor [G-CSF]) to promote WBC recovery. Maximum cumulative doses of the three drugs were approximately 72 mg (V), 40 mg (A), and 28.6 gm/M^2 (C). Drug dose reductions from December 2002 onward are also shown, according to patient age and weight.

RT. RT began at week 3 for most patients with residual microscopic or gross ERMS. Two exceptions were made: subgroup B patients with tumors in vulva, uterus, biliary tract, and superficial nonparameningeal head/neck sites could undergo a delayed primary excision (DPE) at week 12, to remove gross residual tumor. RT was administered after the DPE. Subgroup B patients with vaginal tumors began RT at week 12 if N1 or at week 28 if N0, in an attempt to preserve vaginal tissue and to avoid RT; N0 patients in whom repeated biopsies showed no residual tumor before or by week 28 received no RT.

RT was delivered in conventional fashion using megavoltage equipment, in 1.8 Gy fractions daily for 5 days weekly, with total doses based on the extent of residual tumor and the primary site. Specific total doses were 36 Gy for stage 1 group IIA patients (subgroup A), 45 Gy for stage 1 group III N0 orbit patients (subgroup A), and 36 Gy for stages 2/3 group IIA patients (subgroup B).

Details of the radiation treatments, planning, and results regarding local control will be discussed in a separate publication.

Statistical Considerations

The study design was nonrandomized; results were compared to a fixed expected outcome standard based on similar patients from IRS-III/IV. Treatments were assigned according to subgroup. The primary end point was FFS, defined as the time from study enrollment to disease progression, recurrence, or death as a first event. OS was defined as the time from enrollment to death from any cause. FFS and OS for patients who had not experienced an event were censored at each patient's last date of contact. The Kaplan-Meier method was used to estimate FFS and OS distributions.[8] CI for estimates of time-to-event distributions were calculated using Greenwood's formula.[9] Differences between survival curves were analyzed using the log-rank test.[10] A proportional-hazards model was used to assess independent contributions of potential prognostic factors to predict outcome.[11] Analyses were based on data available by February 2008. Median follow-up among survivors was 5.1 years (range, 0 to 9.9 years); 82% of patients had follow-up of $\geq$ 3 years. *P* values lower than .05 were considered statistically significant.

RESULTS

D9602 accrued 388 ERMS patients (September 1, 1997 to September 17, 2004). The accrual rate was five patients per month, except from September 2002 to December 2002, when subgroup B accrual was suspended because of hepatopathy.[12] Table 1 presents the drug doses and schedules before and after reductions to minimize hepatopathy, most frequent in patients younger than 3 years old.

Eligibility

Forty-six patients (7%) were ineligible: 11 with ineligible pathology, 16 with unavailable pathology, and 19 for other reasons. We report 342 patients with known eligibility and central pathologic review.

Characteristics of Patients/Tumors

The majority of the patients were younger than 10 years of age; 64% were male (male:female = 1.8:1), including 125 with paratesticular tumors (Table 2). One patient was 27 years old; all of the others were younger than 21 years. Most tumors arose in favorable sites (stage 1). Thirty-eight percent had group I disease; 34% had group III disease, mainly orbital tumors; 23% had group IIA tumors, and 5% had groups IIB/C tumors. Most tumors were $\leq$ 5 cm (widest diameter) and noninvasive. Only 5% were N1.

Results for All 342 Patients

The estimated 5-year FFS rate was 88% (95% CI, 84% to 91%); the estimated OS rate was 97% (95% CI, 94% to 98%, Fig 1). At 5 years, cumulative incidence rates of isolated distant metastases were 0.9% (n = 3 patients), of isolated local recurrence 8.5% (n = 28), of isolated regional lymph-node recurrence 0.7% (n = 2), and of combined recurrences, 1.5% (n = 6). Of 28 patients with isolated local recurrence, 11 received primary RT, 15 did not, and two were inevaluable. Of 15 patients with isolated local recurrence who did not receive RT, nine had female genitourinary (GU) tract tumors, two were off therapy before protocol-specified RT, and four received no RT per protocol. Overall, 39 patients developed recurrence; primary sites were orbit (n = 10), head/neck nonorbital (n = 8), vagina (n = 7), paratestis (n = 6), biliary (n = 2), cervix uteri (n = 1), vulva (n = 1), extremity (n = 1), other sites (n = 2), and unknown (n = 1). Thirteen patients died: head/neck (n = 4), orbit (n = 3), biliary (n = 3), and bladder, paratestis, and another site (n = 1 each). Twelve died due to progressive tumor. One of the patients with biliary tumor received chemotherapy and RT, developed severe hepatopathy, and died from *Staphylococcus* sepsis.

Five-year FFS rates were 89% (95% CI, 84% to 92%) in subgroup A patients and 85% (95% CI, 74% to 91%) in subgroup B patients (*P* = .40; Fig 2). Five-year survival rates were similar (Fig 3). In subgroup A, 5-year FFS was 96% (95% CI, 90% to 99%) and OS was 100% for 108 paratesticular patients. Five-year FFS was only 52% (95% CI, 23% to 74%) for 16 girls with GU tumors, but their 5-year OS rate was 92% (95% CI, 57% to 99%). Age and tumor size were not significantly associated with FFS/OS in subgroup A.

Results in 62 subgroup A patients with reduced RT. Stage 1, group IIA, VA and 36 Gy (Table 3). Five-year FFS and OS rates were 81% (95% CI, 68% to 90%) and 94% (95% CI, 83% to 98%). The 5-year cumulative incidence rate of isolated local failure was 15%. Of eight patients with isolated local recurrence, two had primary RT, five females with GU tumors had no primary RT; one was inevaluable. Five-year results of IRS-III and of D9602 for these patients were similar (both received VA), but the IRS-IV patients that received VAC fared better. Because D9602 was designed as a comparison to a fixed standard rather than to IRS-III/IV, *P* values are not appropriate. Based on IRS-III/IV experience, nine failures were expected and 11 occurred (*P* = .50). There was insufficient evidence to conclude that reducing RT from 41.4 to 36 Gy had a negative impact on these patients' outcomes.

Results in 77 patients with orbital tumors with reduced RT. Stage 1, group III, N0, VA and 45 Gy (Table 3). Five-year FFS and OS rates were 86% (95% CI: 76%, 92%) and 96% (95% CI: 87%, 99%). The cumulative 5-year isolated local failure rate was 14%. Of 10 patients with locoregional recurrences, seven had primary RT, two did not; one was inevaluable. There was no evidence to suggest that the reduced RT dose negatively impacted FFS for these patients. Based on IRS-III/IV, 12 failures were expected; 10 occurred (*P* = .56).

Results in 16 subgroup B patients with reduced RT. Stages 2/3, group IIA, VAC and 36 Gy (Table 3). Five-year FFS and OS rates were 94% (95% CI, 63% to 99%) and 100%. One patient with bladder primary tumor did not receive RT and relapsed in retroperitoneum at 10 weeks; the patient was alive 4 years after study entry. IRS-III patients had inferior FFS, OS, and local control rates, probably because they received no alkylating agent(s). IRS-IV patients and D9602 patients fared better. Descriptively, because of small numbers, there was no

Table 2. Characteristics of Patients With Low-Risk ERMS Treated on the D9602 Study With Chemotherapy, With or Without Conventional Radiotherapy (n = 342)*

	Condition and Regimen					
	ERMS/VA (n = 264)		ERMS/VAC (n = 78)		Total (N = 342)	
Characteristic	No.	%	No.	%	No.	%
Age, years						
< 5	94	36	36	46	130	38
5-9	93	35	14	18	107	31
10-14	44	17	19	24	63	18
15+	33	13	9	12	42	12
Sex						
Male	184	70	35	45	219	64
Female	80	30	43	55	123	36
Race/ethnicity						
White	201	77	45	58	246	73
Black	33	13	16	21	49	14
Hispanic	20	8	12	15	32	9
Other	7	3	5	6	12	4
Stage						
1	252	97	55	72	307	91
2	8	3	9	12	17	5
3	0		12	16	12	4
Group						
I	122	47	5	6	127	38
IIA	62	24	16	21	78	23
IIB	0		12	16	12	4
IIC	0		5	6	5	1
III	77	30	39	51	116	34
Primary site						
GU, not B/P						
Paratestis	108	41	17	22	125	37
Other GU	19	7	18	24	37	11
Orbit	96	37	2	3	98	29
Head and neck	29	11	13	17	42	12
Parameningeal	0		3	4	3	1
Extremity	2	1	4	5	6	2
Other sites	7	3	19	25	26	8
Tumor size, cm						
≤ 5	215	83	38	51	253	76
> 5	44	17	37	49	81	24
Invasiveness						
T1 (noninvasive)	246	95	44	59	290	87
T2 (invasive)	13	5	30	41	43	13
Nodal status						
N0	259	99	58	76	317	94
N1	0		17	22	17	5
NX	1	< 1	1	1	2	1

Abbreviations: ERMS, embryonal rhabdomyosarcoma; VA, vincristine and dactinomycin; VAC, vincristine, dactinomycin, cyclophosphamide; GU, not B/P, genitourinary tract, not bladder or prostate; NX, regional lymph node status unknown.
*Some data on race/ethnicity, stage, group, primary site, tumor size and invasiveness, and nodal status were missing in both treatment groups.

evidence to suggest that reduced RT doses negatively impacted FFS for these patients.

Recurrence and Outcome

Subgroup A patients. Twenty-eight of 264 patients relapsed. Twenty-five had local recurrence; six died. Two had regional lymph nodal and distant recurrence; one died at 6.15 years. One had distant metastases and survived. Another patient died with septicemia after severe hepatopathy. Twenty-one patients survived at a median of 3.8 years from relapse (range, 0.02 to 9.5 years).

Subgroup B patients. Eleven of 78 patients relapsed. Three with local recurrence survived, as did one with local recurrence plus regional lymph nodal disease and two with regional lymph nodal recurrence. Two with distant metastases died, as did three with combined locoregional recurrence and distant metastases.

Toxicity

Eight MedWatch adverse event forms were submitted for the eligible patients (2%). Five patients developed hepatopathy, with abdominal distension and right upper quadrant abdominal pain with/

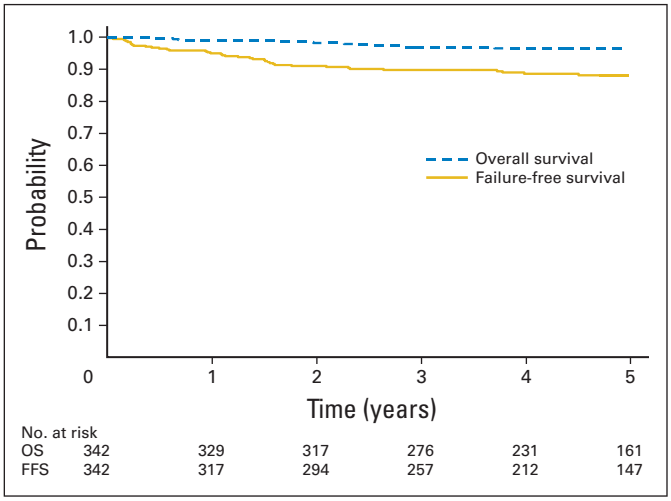

Fig 1. Failure-free survival (FFS) and overall survival (OS), D9602.

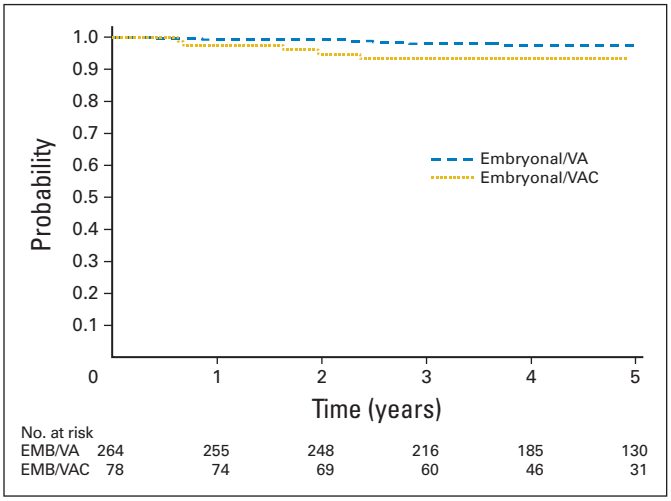

Fig 3. Overall survival, D9602, by subgroups. EMB, embryonal; VA, vincristine and dactinomycin; VAC, vincristine, dactinomycin, and cyclophosphamide.

without other signs of sinusoidal obstruction syndrome[12]; one died of sepsis and the others recovered. After drug dose reductions effected in December 2002, no further cases of hepatopathy were reported. Two patients had severe mucositis. A patient treated with VAC developed hematuria attributed to cyclophosphamide. Rates of decreased absolute neutrophil count lower than 500/μL were 14% to 34% in patients receiving VA and 60% to 95% in patients receiving VAC.

DISCUSSION

Subgroup A patients (n = 264) treated with VA and RT for residual tumor had estimated 5-year rates of 89% (FFS) and 97% (OS). Subgroup B patients (n = 78) had similar results after treatment with VAC and RT for residual tumor: their 5-year FFS rate was 85% and 5-year OS rate was 93%.

We found no evidence that reduced RT dosages for stage 1/group IIA patients and group III orbital patients caused inferior FFS rates, when comparing patients treated with VA, although local control rates were better in similar IRS-IV patients who received VAC without reduced RT. Improved results in IRS-IV may be due to VAC or the combination of VAC with higher RT doses. The results for our patients with stages 2/3 group IIA tumors suggest that cyclophosphamide contributed to the improved outcome, because the D9602 patients who received reduced RT doses fared as well as the IRS-IV patients. D9602 RT doses were based on single-institution studies suggesting efficacy with 30 to 36 Gy for microscopic disease.[5,6] A multicenter trial also supported this approach.[13] Few data exist to define RT dose response below 36 Gy, but eliminating radiotherapy for group II/III patients resulted in high local failure rates.[14,15] Dose reductions in D9602 were purposefully modest so as not to compromise the excellent survival outlook for these patients. Because the RT doses lie on the steep portion of the dose-response curves for many normal-tissue complications, meaningful decreases in long-term morbidity should result.[16-20]

Other cooperative-group studies can be compared to D9602, but involve different patient subsets. The German CWS-86 (Cooperative Weichteil Sarkom Studie) study included 65 patients with localized, completely resected, N0 RMS, synovial sarcoma, and extraosseous Ewing's sarcoma. Their event-free survival (EFS) rate was 83% after treatment with VA, doxorubicin, and ifosfamide for 16 weeks.[13] The 55 lowest-risk patients on the International Society of Pediatric Oncology (SIOP) Malignant Mesenchymal Tumors (MMT) 89 study had completely excised, noninvasive RMS at any site and histology (chiefly ERMS) and included 44 males with localized paratesticular RMS. They received VA in doses similar to our patients but for only 10 weeks, without RT (regimen 89.1). Their 5-year EFS rate was 67% and 5-year OS rate was 87%.[14] These results can be compared to our findings of a 5-year FFS rate of 89% and 5-year OS rate of 97% for subgroup A patients. Our cumulative doses of VA, given over 45 weeks, were much higher than those in the MMT 89 program. However, our subgroup A included patients with microscopic residual tumors and gross residual orbital tumors, so the comparisons are not exact. Nevertheless, one might conclude that a shorter course of VA chemotherapy could be effective in similar future subgroup A patients.

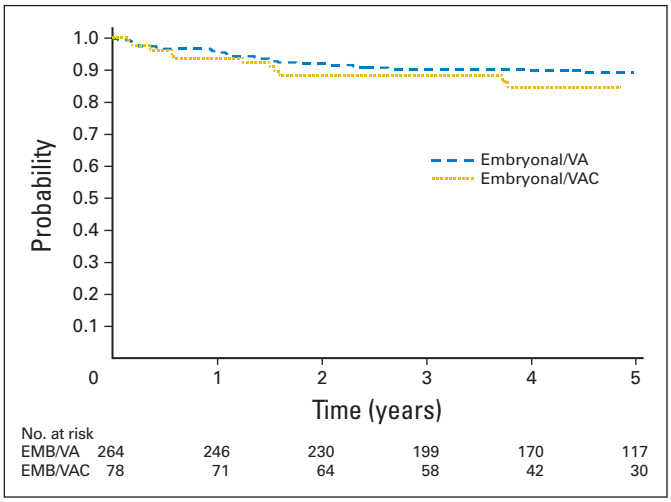

Fig 2. Failure-free survival, D9602, by subgroups. EMB, embryonal; VA, vincristine and dactinomycin; VAC, vincristine, dactinomycin, and cyclophosphamide.

Table 3. Outcomes Among Three Subcategories of D9602 Patients, Compared With Similar Patients From IRSG Protocols III and IV

Parameter	IRS-III		IRS-IV		D9602	
	No.	%	No.	%	No.	%
Stage I, group IIA, No. of patients	52		43		62	
Site of primary tumor						
Orbit	23	44	20	47	18	29
Nonparameningeal head/neck	21	40	7	16	14	23
Paratestis	4	8	11	26	18	29
Other GU, not bladder/prostate	4	8	5	12	11	18
Biliary tract	0		0		1	2
Protocol chemotherapy	VA		VAC/VAI/VIE		VA	
Protocol radiotherapy, Gy	41.4		41.4		36	
5-year failure-free survival		85		98		81
5-year overall survival		94		100		94
5-year cumulative incidence of local-only failure		11		2		15
5-year cumulative incidence of other failure		4		0		4
Group III orbit tumors, No. of patients	71		50		77	
Protocol chemotherapy	VA		VAC/VAI/VIE		VA	
Protocol radiotherapy, Gy	45.0 or 50.4		50.4 or 59.4		45.0	
5-year failure-free survival		79		94		86
5-year overall survival		95		100		96
5-year cumulative incidence of local-only failure		16		4		14
5-year cumulative incidence of other failure		3		0		0
Stages 2 + 3, group IIA, No. of patients	38		28		16	
Site of primary tumor						
Extremity	12	32	4	14	2	13
Retroperitoneum/trunk	9	24	4	14	6	38
Bladder/prostate	6	16	9	32	3	19
Parameningeal	5	13	8	29	3	19
Other	6	16	3	11	2	13
Protocol chemotherapy	VA		VAC/VAI/VIE		VAC	
Protocol radiotherapy, Gy	41.4		41.4		36	
5-year failure-free survival		76		88		94
5-year overall survival		78		92		100
5-year cumulative incidence of local-only failure		14		7		0
5-year cumulative incidence of other failure		11		4		6

Abbreviations: IRSG, Intergroup Rhabdomyosarcoma Study Group; GU, genitourinary tract; VA, vincristine and dactinomycin; VAC, vincristine, dactinomycin, cyclophosphamide; I, ifosfamide; E, etoposide (randomized in IRS-IV).

The SIOP MMT group has focused on patients with localized orbital sarcomas, using multiple-agent chemotherapy to preserve vision and periorbital tissues and avoiding RT in patients whose tumors disappear. This approach was based on the good prognosis for survival and late effects of RT on the eye/orbit. The SIOP-MMT approach without primary RT was compared to primary RT programs for most children with localized orbital rhabdomyosarcoma used in CWS protocols, Italian Cooperative Group protocols, and IRSG protocols.[21] Three hundred six eligible patients were reviewed for EFS and OS at a median of 6.8 years from enrollment. Initially, 72% (n = 222) of the patients had biopsy, 25% partial excision, and 3% complete excision. Eighty percent of the patients were irradiated, including 93% (IRSG), 70% (CWS), 76% (Italian Cooperative Group), but only 37% of the SIOP-MMT patients, those who did not achieve complete remission after chemotherapy. The 10-year actuarial EFS rate was 86% for IRSG patients, compared to 58% to 70% for the other groups ($P < .001$). However, the 10-year OS rate for all patients was 87%, with no significant difference in survival ($P = .67$). OS rates were 86%, whether patients received primary RT or not. Recurrence sites in 51 patients were predominantly local (92%). Late effects consisted mainly of dry eye and impaired vision, almost exclusively in patients treated with RT.[21] Differences in approach regarding the use of primary RT in patients with RMS have been discussed.[22] The 5-year FFS rate of 86% and OS rate of 96% in D9602 orbital patients are comparable with previous IRSG data.

Our subgroup B patients cannot be compared directly with the MMT 89 patients. We administered RT during chemotherapy to patients with residual disease, while the MMT philosophy was to give RT only if local control could not be achieved with chemotherapy followed by surgical removal of residual disease.[21]

It is important that the outcomes of VAC plus RT for residual tumor in subgroup B were similar to VA plus RT for residual tumor in subgroup A. We believe that adding cyclophosphamide improved subgroup B patients' outcome, because they had a worse prognosis, with primary tumors in unfavorable sites and larger than 5 cm in widest diameter.

The challenge remains optimally to balance FFS with OS and toxicity for similar patients. The selected end point in this study was

FFS with the goal to prevent relapse and the subsequent burden of salvage treatment. Thirty-nine of 342 D9602 patients recurred; 29 (74%) survived. Because D9602 had no guidelines for providing salvage therapy, the extent of salvage therapy and long-term complications were not assessed. Still, eliminating cyclophosphamide in subgroup A patients reduced their risk of myelosuppresion and may reduce their long-term risk of infertility and second malignancies. The high total cumulative cyclophosphamide dose given to subgroup B patients, and reducing radiation doses in treatment programs that exclude cyclophosphamide, remain issues to be addressed in future studies, along with assessing the total burden of therapy in patients with recurrent disease.

The currently ongoing study, ARST0331, for patients with low-risk ERMS builds on some of the findings from D9602. The objectives are to achieve the good results of the D9602 approach while decreasing the duration of VA chemotherapy to 22 weeks for subset 1 patients (stages 1/2 groups I/II, stage 1 group III orbit) and adding a total cumulative dose of 4.8 gm/m^2 of cyclophosphamide; to continue using decreased RT doses for patients with orbital and group IIA tumors as in D9602, who receive VA and 4.8 gm/m^2 of cyclophosphamide; and to reduce the dose-intensity of cyclophosphamide to 4.8 gm/m^2 for subset 2 patients (stage 1 group III nonorbit and stage 3 groups I/II).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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